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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/585,503

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Owen P. Hamill

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EXAMINER

HALVORSON, MARK

ART UNIT

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1642

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/585,503	Applicant(s) HAMILL ET AL.	
	Examiner Mark Halvorson	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20-22, 24-30 and 35-42 is/are pending in the application.
- 4a) Of the above claim(s) 24, 25 and 28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20-22, 26, 27, 29, 30 and 35-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/6/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 20-22, 24-30, 35-42 are pending.

Claims 24, 25 and 28 have been withdrawn.

Claims 20-22, 26, 27, 29, 30 and 35-42 are currently under examination.

Objections to Specification withdrawn

The objections to the specification are withdrawn in view of Applicant's amendments to the Specification.

Objections to Claim withdrawn

The objection to claim 29 is withdrawn in view of Applicants amendment to claim 29.

35 USC § 112 1st paragraph rejection maintained

The rejection of claims 20-22, 26, 27, 29, 30 and new claims 35-42 for failing to comply with the enablement requirement is maintained.

Applicants argue that two of the documents used to demonstrate lack of enablement, Gottlieb et al, and Dietrich et al, were published after the filing date of the present application and are therefore it is improper to use Gottlieb et al, and Dietrich et al to demonstrate a lack of enablement. M.P.E.P. §2154.05(a). Applicants cite In re Hogan, 559 F.2d 595,194 USPQ 527 (CCPA 1977), in which Applicants argue that the CCPA expressed concern that subsequently generated art could be used to attack patents and thus hinder early disclosure. Applicants argue that there are only limited exceptions to this rule, such as the use of post-filing art to demonstrate that one of ordinary skill in the art would not have reasonably believed the prophetic teachings of a specification as of its filing date. Applicants argue that Gottlieb et al. (2008) and Dietrich et al. (2007) do not include evidence demonstrating that one of ordinary skill in the art

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would not have reasonably believed the prophetic teachings of the present specification as of its filing date.

Applicants' arguments have been considered but are not persuasive. MPEP 2164.05(a) does not state that it is improper to use post-filing art to demonstrate a lack of enablement. MPEP 2164.05(a) discloses

In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In *re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms.

Thus, the use of Gottlieb et al and Dietrich et al to demonstrate a lack of enablement was proper because both Gottlieb et al and Dietrich et al support the contention that the role of the MscCa channel in cancer was unknown at the time of the filing of the present application, and in fact, was still unknown three years after the filing date of the present application. This state of the art at the time of filing is one factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph. Thus, the use of Gottlieb et al, and Dietrich et al to demonstrate a lack of enablement is proper to demonstrate the state of the art in regards to the role of the MscCa channel in cancer at the time of filing of the present application.

Furthermore, *In re Hogan* concerned the post-filing discovery of an amorphous polymer and therefore the use of post-filing art in *In re Hogan* is clearly distinct from the use of post-filing art in the current 35 USC 112 rejection. The court in *In re Hogan* stated that "this court has approved use of later publications as evidence of the state of

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art existing on the filing date of an application". (In re Hogan, 194 USPQ 527, 537 (CCPA 1977)).

Applicants further argue that the teachings of Verrall et al. showing increased migration of prostate cancer cells are irrelevant when considering enablement of the pending claims. Applicants argue that there are technical concerns regarding Verrall et al in that it has been shown by Caldwell et al that the trivalent cation Gd^{3+} is highly chelated by inorganic and organic multivalent anions, such as the anions present in serum, so that free Gd^{3+} approaches diminishing low concentrations. Applicants argue that Verrall et al. dissolved Gd^{3+} in medium supplemented with 1% fetal calf serum.

However, Caldwell et al also states that the trivalent cation Gd^{3+} may be chelated by phosphate or bicarbonate-buffered solutions. (Abstract) It is noted that the medium used by Applicants is RPMI-1640, which are buffered with a bicarbonate solution. Furthermore, the explanation by Applicants would suggest that chelated Gd^{3+} acts completely opposite that of unchelated Gd^{3+} . Clearly, Applicants results are in conflict with Verrall et al and there may be a technical reason for the opposing results. But whatever the reason, the results of Verrall contradict the results of Applicants and are part of the analysis as to whether the claims of the present application are enabled.

Applicants also argue that the specification teaches methods of separately using four different agents (Gd^{3+} , GsMTx-4, anti-TRPC1 antibody, and an siRNA for TRPC1) to decrease activity of a mechanosensitive Ca^{2+} -permeable (MscCa) channel. Examples 5 and 6 show the four agents decreased migration in PC3 cells. Applicants argue that Applicants have done precisely what Gura recommends as a potentially "easy way to identify promising cancer drugs." Applicants argue that despite the earlier teachings of Freshey (1 983) and Derrner (1994), Zips et al. (2005) recognizes that *in vitro* tumor models continue to be useful and relevant in the analysis of anticancer agents. Applicants further argue that the further evaluation of promising anticancer agents using *in vivo* animal models is routine. Applicants also argue that enablement is not precluded by the necessity for some experimentation, such as routine screening. Applicants argue that screening agents that decrease MscCa channel activity in *in vivo*

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animal models does not constitute "undue experimentation," particularly in an art where the level of skill is high.

Applicants arguments have been considered but are not persuasive. Applicants have demonstrated *in vitro* that agents that decrease activity of a mechanosensitive Ca^{2+} -permeable (MscCa) channel inhibit migration of a cell line. As previously mentioned, Zips et al (*In Vivo*, 2005, 19:1-7).state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential." Guru, White et al and Young et al disclose the unpredictability of cancer therapy using antibodies. Gottlieb et al and Dietrich et al disclose that the importance of the MscCa channel in cancer was unknown at the time of filing.

Given the disclosure of the specification that discloses only *in vitro* results, the teaching in the art that indicates the unpredictability of treating cancer with antibodies and the teaching in the art that indicates uncertainty on the role of the MscCa channel in cancer, one skilled in the art could not predictably treat cancer *in vivo* with inhibitors of the MscCa channel, including antibodies to TRPC1.

Applicants have added claim 37 to indicate an *ex vivo* treatment. It is unclear how the administration of a cell which has been treated *ex vivo* with an agent that decreases activity of a mechanosensitive Ca^{2+} channel can be used to treat cancer, decrease metastasis or decrease symptoms associated with cancer.

Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

35 USC § 102(b) rejections withdrawn

The rejection of claims 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al, (US Patent No: 6, 214, 824, issued April 10, 2001) is withdrawn in view of Applicants amendments to claims 20-22

NEW REJECTIONS: Based on the Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 21, 22, 35 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

There is no support in the specification as filed for the limitation “wherein the cell is ex vivo” as it relates to a method of treating cancer comprising administering a composition comprising an agent that decreases the activity of a mechanosensitive Ca²⁺ permeable channel present on the cancer cell. The only disclosure in the specification concerning ex vivo use is to evaluate agents in ex vivo models. (page 25, lines 25-27).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37 and 38 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites the limitation "wherein the cell is ex vivo". Claim 38 recites the limitation "wherein the cell is in vivo". There is insufficient antecedent basis for the term "cell" in claims 20-22

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al, (US Patent No: 6, 214, 824, issued April 10, 2001) as evidenced by Nazarenko et al (Microbiology, 2003, 149:1147-1153).

The claims are drawn to a method for treating cancer, decreasing metastasis of a cancer and decreasing a symptom associated with cancer comprising administering to a subject having cancer an effective amount of a composition comprising an agent that decreases activity of a mechanosensitive Ca^{2+} channel present on a cancer cell.

Evan et al discloses a method of treating cancer comprising administering to the host an amount of amiloride. (claim 1). As evidence by Nazareno et al amiloride inhibits the activity of the mechanosensitive Ca^{2+} channel (page 1150, 2nd column). Furthermore, Applicants state that amiloride mechanosensitive Ca^{2+} channels. Thus, the inhibition of mechanosensitive Ca^{2+} channels would be an inherent property of amiloride and a method of treatment comprising administering amiloride would read on claims drawn to a method of inhibiting cancer comprising administering an agent that inhibits mechanosensitive Ca^{2+} channels.

Summary

Claims 20-22, 26, 27, 29, 30 and 35-42 stand rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Mark Halvorson
Patent Examiner
571-272-6539

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Primary Examiner, Art Unit 1642